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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/127,738	08/03/1998	F. ABEL PONCE DE LEON	002076-005	1682

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/127,738	PONCE DE LEON ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-17-03 has been entered.

The amendment filed 3-17-03 has been entered as requested. Applicant's arguments filed therein have been fully considered but they are not persuasive. No new rejections are set forth in this advisory action. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 5, 9, 10, 12, 13, 16-19, 21-23 and 30 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) a method of obtaining avian EG cells comprising: i) isolating PGCs from an avian embryo; and ii) culturing said PGCs in a culture medium comprising LIF, bFGF and IGF, such that avian EG cells are obtained; 2) a method of making a germline chimera to test a population of PGCs for EG cells comprising: i) isolating PGCs from an avian embryo; ii) culturing said PGCs in a culture medium comprising: LIF, bFGF and IGF; iii) transferring said PGCs into a

recipient avian embryo; and iv) obtaining a chimeric avian, wherein a germline chimeric avian indicates EG cells were obtained, does not reasonably provide enablement for 1) identifying avian EG cells in a mixed population of avian EG cells and PGCs using mouse stage specific antigen 1, EMA-1 or MC-480, 2) stably transfecting avian EG cells, 3) a method of making germline chimeric avians expressing exogenous proteins or having a non-wild-type phenotype; 4) obtaining turkey EG cells; or 5) a method of making a somatic cell chimeric avian that is not a germline chimeric avian. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claim 9 requires obtaining EG cells that produce mouse-stage specific antigen 1, and/or reacts with EMA-1 or MC-480 antibody. While the specification enables obtaining EG cells as determined by obtaining germline chimeric chickens (pg 37, line 13), the specification does not enable obtaining avian EG cells having the markers claimed. Pain of record taught obtaining EG cells from Stage X embryos within a mixed population of PGCs and EG cells that provide germline and somatic cell transmission. Pain taught marker proteins found on the mixed population of cells but did not teach the pattern that distinguishes EG cells from PGCs (pg 2345, col. 2). Similarly, the specification defines EG cells as being able to produce germline and somatic cell chimeras (pg 22, lines 15-21) and teaches administering a mixed population of PGCs and EG cells to a recipient embryo (pg 33, line 5). While the specification discusses the staining

pattern of EG cells relating to SSEA-1 and 3 marker proteins, and reactivity with EMA-1 and MC-480 antibodies (pg 21, line 16 through pg 22, line 9), the specification does not provide adequate correlation between staining of SSEA-1 and 3 proteins, or reactivity with EMA-1 and MC-480 antibodies and the ability to produce germline and somatic cell chimeras such that EG cells could be distinguished from PGCs. EMA-1 is not specific to EG cells because it also stains PGCs (pg 22, line 1).

Applicants argue that MC-480 reacts strongly with mouse EG cells and avian EG cells cultured after 98 days and weakly with PGCs. Applicants' argument is not persuasive because both avian EG cells and PGCs react with MC-480 (pg 42, lines 4-7). The specification does not teach how "strongly" MC-480 must react for a cell to be an avian EG cell.

Claim 10 remains rejected because merely transferring the mixed population of cells to a suitable avian embryo is not adequate to determine whether EG cells have been obtained. Transferring the mixed population of cells into an embryo and obtaining somatic cell chimeras that are not germline cell chimeras does not have an enabled use in the instant invention. Applicants have not addressed this rejection.

Claim 30 is directed toward making a germline or somatic cell chimeric avian. The claim encompasses making a somatic cell chimeric avian that is not a germline chimeric avian. The specification does not provide an enabled use for making a somatic cell chimeric avian that is not a germline chimeric avian for reasons of record. While making a germline chimeric avian is used to confirm

whether a population of PGCs has EG cells, making a somatic cell chimeric avian does not have a disclosed use in the specification. Applicants argue somatic chimeras have a well-known use in the art for studying avian development and the interactions of genetically different cell types within an individual and cite Wantanabe. Applicants' argument is not persuasive. Such a use is not disclosed in the specification and is not readily apparent. Studying avian development is a generic use and is not specific to somatic chimeras. It cannot be envisioned why one of skill would monitor the interaction of genetically different cell types within a chimera. Applicants argue somatic cell chimeras can be used as food. Applicants' argument is not persuasive because using the avian for food is not specific to the chimeric avian. The asserted enabled uses for making somatic cell chimeric avians cannot be found in the specification and do not have a specific utility. Therefore, claim 30 should limited to making a germline chimeric avian.

Claims 12, 13, 22 and 23 require transfecting EG cells with a nucleic acid sequence. Claims 17-19 and 21 require transferring EG cells transfected with a nucleic acid sequence into a embryo to make a germline chimeric avian. The claims remain rejected because the specification does not enable transfecting or transforming EG cells with a nucleic acid for reasons of record. The only disclosed purpose for transfecting avian EG cells is to make transgenic avians expressing exogenous proteins or having an altered phenotype (pg 7, line 17; pg 2, line 23).

Specifically, the specification does not enable transfecting EG cells with DNA encoding a growth factor or enzyme (claims 21 and 23) or isolating an exogenous protein from the egg, systemic circulating system, body fluid or tissue of a chimeric avian (claims 19 and 22). The state of the art at the time of filing was such that the phenotype of transgenic avians with an exogenous transgene was unpredictable (Wall of record, 1996, Theriogenology, Vol. 45, pg 57-68; ¶ bridging pg 61-62). The specification does not provide adequate guidance for one of skill to reasonable predict that the DNA encoding exogenous proteins would be functionally expressed in transgenic avians, where exogenous protein would be expressed in transgenic avians or that the exogenous protein would have a therapeutic effect. Given the unpredictability in the art taken the teachings provided, the specification does not enable transfecting EG cells with DNA encoding a therapeutic protein or determining whether exogenous protein would be expressed in the egg, systemic circulating system, body fluid or tissue of a chimeric avian.

Applicants argue that despite the unpredictability in the art for one of skill to express a transgene or to stably transfect EG cells, it would not have required undue experimentation for one of skill to make or use the claimed invention (pg 11, line 1 of response). Applicants argue the avians of Vick could be used for studying reproductive biology because transfected cells can be distinguished from non-transfected cells (pg 11, 4 lines from the bottom). Applicants' arguments are not persuasive. Again, the only use for making EG cells and transfecting them with a nucleic acid sequence is to make a germline chimeric

avian whose genome comprises a transgene and functionally expresses the transgene. The specification does not provide a use for transfecting EG cells as in claims 12, 13, 22 and 23 wherein non-stable transfection occurs or for using non-stably transfected EG cells to make chimeras. The art did not teach how to stably transfect EG cells or making such a germline chimeric avian. Nor does the specification teach how to do so. Therefore, it would have required one of skill undue experimentation to transfect EG cells as claimed. It cannot be envisioned how distinguishing transfected and non-transfected cells in the gonad reveals anything about reproductive biology. The purpose of Vick is to make a germline chimera that passes on the transgene to its offspring. Failure to obtain such an avian is a clear indication that undue experimentation would be required for one of skill to obtain a germline chimera. Merely transplanting transfected cells into an embryo without expressing the transgene or without passing the transgene on to offspring does not have an enabled use in Vick or elsewhere in the art at the time of filing.

Applicants argue Vick in view of Bosselman and Lee enable one of skill to transfect EG cells and obtain germline chimeric avians as claimed. Applicants argument is not persuasive because Vick, Bosselman and Lee do not teach how to obtain stably transfected EG cells or how to use transfected EG cells to obtain a germline chimeric avian. The examiner does not disagree that it may be possible one day to use transfected EG to make a germline chimeric avian; however, the art at the time of filing taken with the guidance provided in the

specification would still leave the person of skill in the art with undue experimentation to determine the parameters required to do so.

Applicants point to a number of references on pg 15-17, none of which teach culturing PGCs and obtaining EG cells, transfecting EG cells with a transgene and obtaining a germline chimeric avian whose genome comprises the transgene and functionally expresses the transgene. Applicants mischaracterize Naito who did not transfect PGCs in culture; Naito injected DNA directly into an embryo.

Claims 1-23 and 25-30 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The metes and bounds of what applicants consider PGCs cannot be determined. Applicants previously argued the specification distinguishes avian PGCs from avian EG cells in that avian EG cells stain positive for MC-480 (as well as SSEA-1, SSEA-3 and EMA-1 also found of PGCs) and provide germline and somatic cell transmission upon implantation into recipient embryos while avian PGCs do not stain positive for MC-480 and do not provide somatic cell transmission (pg 21, line 13 through pg 22, line 21). Applicants' argument was not persuasive because PGCs stain positive for MC-480 (pg 42, lines 4-7). It cannot be determined what amount of positive staining distinguishes PGCs and

EG cells. Therefore, the metes and bounds of cells that are EG cells within a population of PGCs cultured for a period of time in the presence of LIF, bFGF, SCF and IGF are avian EG cells cannot be determined.

Applicants address this rejection on pg 19 of the response but do not discuss the metes and bounds of PGCs. Applicants state identification of specific EG cells or PGCs would not be required. Applicants' argument is not persuasive because claim 1, step (i), for example, requires isolating PGCs. It is unclear if a the step is limited to isolating PGCs that become EG cells or if the claim encompasses isolating a population of cells comprising PGCs and EG cells

Claims 14, 26 and 30 as newly amended are indefinite because the phrase "cells produced by step (ii) comprising EG cells" is unclear. Step (ii) merely requires that the time the PGCs are in culture is sufficient to produce EG cells; step (ii) does not require producing EG cells. Therefore, the cells in step (ii) may not have EG cells as required in step (iii). In addition the phrase "said cells produced by step (ii) comprising EG cells" (claim 30) lacks antecedent basis.

The phrase "said transferred EG cells" in claims 26 and 30 lacks antecedent basis.

Claim Rejections - 35 USC § 102

Claims 1, 4-11, 14-16 and 20 remain rejected under 35 U.S.C. 102(b) as being anticipated by Pain (7-25-96, Development, Vol. 122, pages 2339-2348, UnCover online at http://uncweb.carl.org/uncover/unchome.html) as evidenced by Simkiss (Simkiss, 1994, MacLean, ed., Animals with novel genes, Transgenic birds, Cambridge Univ. Press, Cambridge England, NY, NY, pages 106-137) and under 35 U.S.C. 102(a) as being anticipated by Pain (Aug. 1996, Development, Vol. 122, pages 2239-2348) as evidenced by Simkiss (Simkiss, 1994, MacLean, ed., Animals with novel genes, Transgenic birds, Cambridge Univ. Press, Cambridge England, NY, NY, pages 106-137) for reasons of record.

Pain taught isolating cells from the blastoderm of a stage X chicken embryo, culturing the cells for more than 160 days in the presence of bFGF, IGF,

SCF, LIF without feeder cells (pg 2340, col. 1, line 9; pg 2340, col. 1, 4th and 5th full ¶; pg 2345, col. 2, line 10; 2341, col. 2, ¶ 4). The cells expressed EMA-1, SSEA-1 and SSEA-3 for 160 days (pg 243, col. 2, last 2 sentences). Simkiss confirms the cells of Pain included PGCs by teaching stage X chicken embryos contain PGCs (pg 111, Fig. 4.1, top panel). Pain taught introducing the population of cells into stage X chicken embryos and obtaining germline and somatic cell chimeras (pg 2341, col. 1, ¶ 2; pg 2346, col. 2, line 8).

Applicants argue Pain does not teach culturing PGCs for at least 14 days in the absence of feeder cells. Applicants' argument is not persuasive. Claims 1, 4-7, 9-11, 14-16 and 20 do not require culturing PGCs for at least 14 days. Pain clearly obtained EG cells and showed that undifferentiated avian cells were maintained for 5 days in the absence of feeder cells (pg 2340, col. 1). Claims 6-8 are included because Pain taught culturing the cells for more than 160 days in the presence feeder cells (pg 2343, col. 2, 4 lines from the bottom), Pain obtained germline chimeras (proof of the presence of EG cells) and Pain taught "the cultures" were maintained with or without feeder cells (pg 2341, col. 2, para. 4). Therefore, Pain taught any of the cultures, including PGCs having EG cells cultured for 160 days (pg 2345), can be cultured without feeder cells.

Applicants argue Pain taught away from long-term culture in the absence of feeder cells. Applicants' argument is not persuasive. The claims do not require "long term culture." While Pain taught feeder cells were used, Pain did not teach they were preferred. Pain taught cultures could be made with or without feeder cells. By culturing cells for 160 days with feeder cells, Pain did not

"teach away" from culturing without feeder cells. Pain does not state a culture without feeder cells cannot be maintained or discourage one of skill to culture without feeder cells.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4-11, 14-16 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pain (Aug. 1996, Development, Vol. 122, pages 2239-2348) as evidenced by Simkiss (Simkiss, 1994, MacLean, ed., Animals with novel genes, Transgenic birds, Cambridge Univ. Press, Cambridge England, NY, NY, pages 106-137).

Pain taught isolating cells from the blastoderm of a stage X chicken embryo, culturing the cells for more than 160 days in the presence of 10 ng/ml bFGF, 20 ng/ml IGF, 1% vol/vol SCF, 1% vol/vol LIF without feeder cells (page 2340, col. 1, line 9; page 2340, col. 1, 4th and 5th full paragraphs; page 2345, col. 2, line 10; 2341, col. 2, paragraph 4). The cells expressed EMA-1, SSEA-1 and SSEA-3 for 160 days (page 243, col. 2, last 2 sentences). Simkiss confirms that isolating cells from the blastoderm of stage X chicken embryos of Pain results in isolating some PGCs as claimed by teaching that stage X chicken embryos contain PGCs (page 111, Fig. 4.1, top panel). Pain teaches introducing the cultured PGCs into stage X chicken embryos and obtaining germline and somatic cell chimeras (page 2341, col. 1, paragraph 2; page 2346, col. 2, line 8). The ES cells of Pain are EG cells as claimed because they produce germline and somatic cell chimeric chicks. Obtaining ES cells capable of making germline

chimeras as taught by Pain is equivalent to obtaining EG cells (claim 1). Pain does not teach using 0.00625 U/μl LIF, 0.25 pg/μl bFGF, 0.5625 pg/μl IGF, 5.0 pg/μl SCF as in claim 2.

However, Pain taught varying the culture conditions required to obtain EG/ES cells (page 2341, col. 2, "Requirements of specific growth factors and cytokines for CEC and QEC cells"). One of ordinary skill in the art at the time the invention was made would have motivated to use 0.00625 U/μl LIF, 0.25 pg/μl bFGF, 0.5625 pg/μl IGF, 5.0 pg/μl SCF to optimize the conditions required to obtain EG/ES cells.

Applicants reiterate their arguments regarding Pain, which have been addressed above.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120. The Examiner's number will be changed on January 12th, 2004 to 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER